THE UNIVERSITY OF ALBERTA

I. A TOTAL SYNTHESIS OF α-DAMASCONES.
II. SYNTHETIC STUDIES ON FUKINANOLIDE.

by

© GEORGE LUKANDO MHEHE

A THESIS

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

I. A TOTAL SYNTHESIS OF α-DAMASCONES

II. SYNTHETIC STUDIES ON FUKINANOLIDE

submitted by GEORGE LUKANDO MHEHE in partial fulfilment of the requirements for the degree of Master of Science.

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Supervisor

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.....

Date Aug. 23, 1976

TO EDITH AND OUR TRIPLETS:-

MSAFIRI, TUMAINI AND ZAWADI

ABSTRACT

A total synthesis of cis- (3a) and trans-α-damascone (3b) has been accomplished. A mixture of 4-carbethoxy-3,5,5-trimethyl-2-cyclohexen-1-one (16) and its positional isomer 17 was obtained from the boron trifluoride catalysed condensation of acetone and ethyl acetoacetate according to the reported procedure. Treatment of the mixture with 1,2-ethanedithiol and borontrifluoride etherate at 0°C resulted in the exclusive formation of the desired thioketal ester 18 and complete recovery of 17. Lithium aluminum hydride reduction of 18 followed by Moffatt oxidation of the resulting alcohol 20 gave aldehyde 22 which on treatment with a mixture of cis and trans-1-propenyl magnesium bromide afforded trans-thioketal alcohol 23 and cis-thioketal alcohol 24. Manganese dioxide oxidation of 23 followed by desulfurization of the resulting enone 25 using deactivated W-2 Raney nickel gave trans-α-damascone (3b). Similarly, 24 was converted to cis-α-damascone (3a) via intermediate 26. Details of the synthesis are described in Chapter I of this thesis.

The second chapter describes the preparation of keto ester 15, a potential synthetic precursor of fukinanolide (1), from 3,4-dimethyl-2-cyclohexen-1-one. Photocycloaddition of this enone to vinyl acetate in benzene gave a diastereomeric mixture of adduct 17 which

upon treatment with aqueous sodium hydroxide in methanol afforded keto alcohol 18. Thioketalization of 18 and the desulfurization of the resulting thioketal alcohol were carried out under general reaction conditions. The alcohol 20 thus obtained was subsequently subjected to Moffatt oxidation to give ketone 22 and its C-5 epimer 21. Ring expansion of 22 with ethyl diazoacetate using boron trifluoride etherate as a catalyst resulted in the formation of 15.

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TABLE OF CONTENTS

Page

ABSTRACT v

ACKNOWLEDGMENTS vii

LIST OF SCHEMES ix

CHAPTER

I. A TOTAL SYNTHESIS OF α-DAMASCONES

Introduction 1

Results and Discussion 7

Experimental 16

References 26

II. SYNTHETIC STUDIES ON FUKINANOLIDE

Introduction 28

Results and Discussion 34

Experimental 43

References 51

LIST OF SCHEMES

Page

SCHEME I 31

INTRODUCTION

In 1970, Demole and his co-workers reported the isolation of β-damascenone (1) in minute quantity from Bulgarian rose oil (Rosa damascena Mill.) (1). It has since been found as a trace component in Burley tobacco oil (2) and in other natural materials (3-5). This naturally occurring ketone has an exceptionally powerful as well as pleasing odor and it could become a key substance in modern fragrances (1). Because of its industrial importance and limited availability from natural sources, much attention has been drawn to the synthesis of this odoriferous ketone as well as to that of its structurally related compounds.

Shortly after its isolation, β-damascenone (1) and its four dihydro-derivatives, cis-β-damascone (2a), trans-β-damascone (2b)[1], cis-α-damascone (3a) and trans-α-damascone (3b) were synthesized by Demole, et al., starting from α- (4) and β-cyclocitral (5) (1).

In 1971, two additional dihydro compounds, γ-damascones (6a and 6b), were prepared by a group at Firmenich & Co. using two different routes (7). One of the routes was based on the Wharton rearrangement (8)

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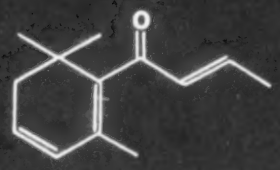
[1] trans-β-Damascone (2b) has since been isolated from several natural sources (2, 6). The other damascones are yet to be uncovered from nature.



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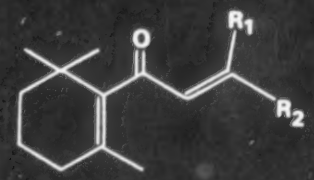

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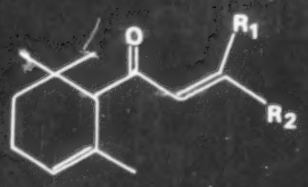

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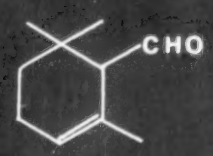

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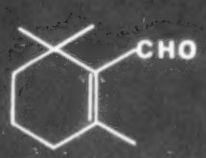

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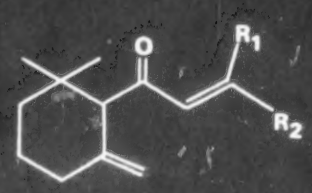


6a $R_1 = CH_3$; $R_2 = H$

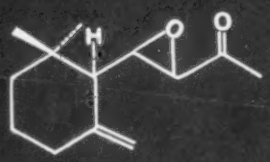
6b $R_1 = H$; $R_2 = CH_3$

of epoxy-γ-dihydroiononones (7a and 7b) whereas in the alternative procedure, the Wittig rearrangement of butinyl ether 8 served as a key step.

A new synthesis of 1 along with its α-isomer 9 was developed in 1971 by Büchi and Wüest involving ethyl α-sufranate (10a) and ethyl β-sufranate (10b) as key intermediates (9).

The fact that damascones are closely structurally related to α- (11a), β- (11b) and γ-ionone (11c) led many research groups to investigate the possibility of interchanging the conjugated enone functionality of the readily available ionones as a means for the synthesis of the corresponding damascones. In addition to the previously cited case, Büchi and Vederas (10) as well as Ohloff and his co-workers (11) were able to achieve such transformations in good yields via isoxazole intermediates, e.g. β-ionone isoxazole 12 and Rautenstrauch used the Meisenheimer rearrangement (11) of N-oxide 13 as a key reaction in his transformation of α-ionone to 3b (12).

Diels-Alder reaction which allows the formation of cyclohexenes in a simple manner is obviously useful in the construction of β-damascenone (1) and its related compounds. Cookson and his co-workers used the aluminum chloride catalyzed Diels-Alder addition of 1,3-pentadiene to 3-bromo-4-methyl-3-penten-2-one and to mesityl oxide



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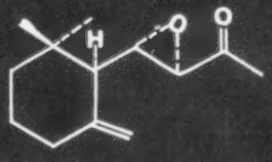

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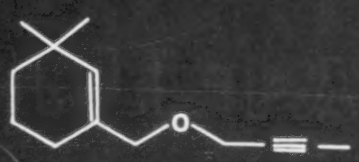

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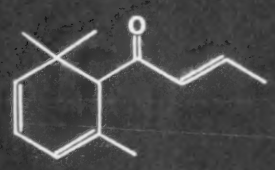

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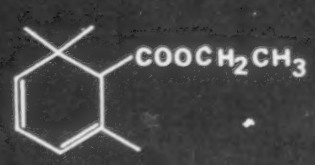

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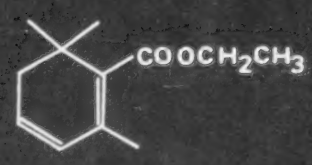
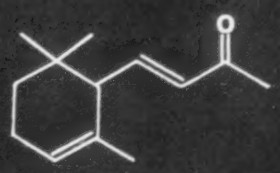


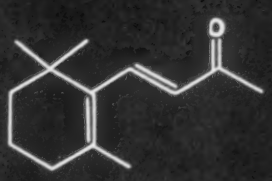
10b

as the initial step in their synthesis of β-damascenone (1) and δ-damascone (14) respectively (13). An alternative Diels-Alder route has also been developed for the synthesis of 14 by Dauben, Kozikowski and Zimmerman using olefin 15 as an dienophile (14).

Although several syntheses of damascenones and damascones are available, the existing methods for constructing α-damascones (3a and 3b) require, as discussed previously, modifications of α-cyclocitral (4) or α-ionone (11a). The purpose of the present studies is to achieve an efficient total synthesis of these two industrially important ketones without relay and first part of this thesis describes such a total synthesis.



11a



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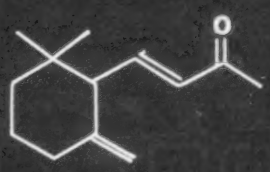

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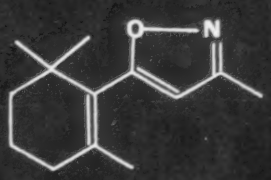

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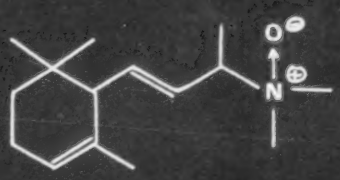

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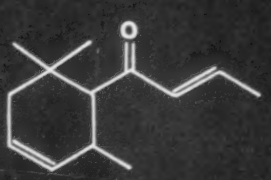

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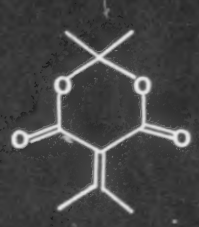

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RESULTS AND DISCUSSION

For the present synthesis, keto ester 16 was used as the starting compound. The material so chosen has clearly the advantages that the three methyl groups of the target molecules cis- (3a) and trans-α-damascone (3b) are present and its functionalities are located at ideal positions for subsequent modification. Several methods were reported for the preparation of 16 (15-18). The procedure of Rubinstein (15) was adapted for its simplicity. Although it was reported that a single isomer was obtained, the boron trifluoride condensation of acetone and ethyl acetoacetate under the described conditions gave, in our hand, a mixture of the desired keto ester 16 and its positional isomer 17 in a ratio of ca. 2:1. Attempts to separate these two isomers by distillation were fruitless. A similar mixture was also obtained previously by Surmatis et al. (18) using zinc chloride as a catalyst. They found that 17 could be selectively hydrolyzed by heating the mixture with zinc chloride in ethanol and water to facilitate the separation of 16.

Efforts made toward this end did not result in any noticeable change of the mixture composition. The two isomers however were separable as noted (18) by extensive column chromatography on silica gel and the pure 16 and 17 thus obtained showed spectral data[2]

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[2] See experimental section for details of spectral data.

identical with those cited in the literature (18).

Subsequently, the ketone carbonyl was converted into a thioketal group for dual purposes. In addition to serving an intermediate for the necessary removal of the ketone carbonyl at an appropriate stage, the thioketal group was expected to facilitate the preservation of the location of the double bond on the basis of the previous findings in this laboratory that the presence of an adjacent thioketal group increased considerably the stability of a double bond (19). The thioketalization of 16 was effected by its treatment with excess of 1,2-ethanedithiol using boron trifluoride etherate as catalyst to give thioketal ester 18 whose infrared (ir) spectrum showed the characteristic ester and double bond absorption bands at 1732 and 1665 cm^{-1} respectively and the complete absence of that of a ketone carbonyl. In the nuclear magnetic resonance (nmr) spectrum, the four thioketal hydrogen atoms resonated at δ 3.28 as a singlet. Furthermore, a vinylic proton appeared at δ 5.63 as a broad singlet clearly indicating the presence of a trisubstituted double bond and, consequently, its location. The structural assignment of 18 was further confirmed by the mass spectrum displaying a molecular ion peak at 286.10606. Similarly, thioketalization of 17 gave the corresponding thioketal 19.

At this point, since the separation of 16 and 17

was rather time-consuming and since the ketalization products appeared to be more separable than their precursors on silica gel thin-layer chromatography, it was considered to be more efficient to carry the mixture to the thioketal stage and to isolate the desired ketal ester 18 thereafter. Consequently, a mixture of 16 and 17 was treated with boron trifluoride and 1,2-ethanedithiol at room temperature and it was observed during the reaction that the latter isomer proceeded the thioketalization slower than did the former one. This finding indicated the possibility that 16 might undergo selective thioketalization under suitable reaction conditions. Indeed, when the reaction temperature was lowered to 0°C, 16 underwent thioketal formation exclusively and quantitatively after seven hours whereas 17 remained totally unreacted.

To convert 18 into 3a and 3b, it requires the removal of the thioketal group and the modification of the ester substituent. The required side chain was first installed. Lithium aluminum hydride reduction of 18 afforded, in 82% yield, crystalline alcohol 20, m.p. 46-7°C. Its ir spectrum showed the absorption bands at 3430 and 1650 cm^{-1} for the hydroxyl group and the double bond respectively. The nmr spectrum displayed two multiplets at δ 5.64 and 3.65 for the olefinic and the hydroxymethylene protons respectively and a singlet at

δ 3.26 for a total of four thioketal methylene protons. Alcohol 20 was found to be rather unstable. In one of the experiments, it underwent complete dehydration to give diene 21[3], when a solution of 20 in chloroform was allowed to stand over magnesium sulfate at room temperature overnight. Even in pure state and at 0°C, it deteriorated to certain extent over a period of storage. Attempted Moffatt oxidation of 20 using dicyclohexylcarbodiimide, dimethyl sulfoxide, trifluoroacetic acid and pyridine (20) produced, in addition to the desired aldehyde 22, a substantial quantity of the dehydration product 21. The oxidation proceeded smoothly however when phosphoric acid (21) was substituted for trifluoroacetic acid and pyridine and an 80% yield of 22, m.p. 62-3°C was obtained. The ir spectrum showed, in addition to the double bond absorption at 1648 cm^{-1}, the diagnostic aldehyde bands at 2830, 2710 and 1715 cm^{-1} whereas in the nmr spectrum the aldehydic proton appeared at δ 9.39 as a doublet. A molecular ion in the mass spectrum at 242.0799 was in accord with the assigned structure.

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[3] Diene 21 showed the following spectral data: ir (film) 1670 and 1598 cm^{-1} (double bonds); nmr (CCl_4) δ 5.63, (broad s, 1H, $=\overset{|}{C}H$), 4.88 (broad s, 2H, $=CH_2$), 3.18 (s, 4H, $-SCH_2CH_2S-$), 2.17 (s, 2H, $-CH_2-$), 1.73 (d, 3H, J = 1.5 Hz, $=CCH_3$), 0.90 (s, 6H, $-C(CH_3)_2$); mass spectrum M^+ 226.08496 (calcd. for $C_{12}H_{18}S_2$: 226.08519).

Subsequent incorporation of a propenyl group was effected by treatment of 22 with propenyl magnesium bromide prepared from a mixture of cis- and trans-1-bromopropene according to the reported procedure (1) to give two isomeric alcohols 23 and 24 (m.p. 93-4°C)[4] in approximately equal amounts with a total yield of 93%. Their structures were readily assigned on the basis of the spectral data. The isomeric nature of these two compounds was clearly indicated by the mass spectra displaying in each case a molecular ion peak in agreement with a molecular formula of $C_{15}H_{24}OS_2$. In the nmr spectra the newly introduced vinylic protons appeared as a doublet in both cases at δ 5.52 and 5.38 for 23 and 24 respectively. In the ir spectra, a strong hydroxyl absorption band was observed in each case. The stereochemistry of these two isomers, however, could not be determined with absolute certainty on the basis of the information available at this point. These assignments follow from the subsequent transformations.

The conversion of 23 to 3b and 24 to 3a could be achieved in principle by first removing the thioketal moiety and then oxidizing the hydroxyl group to a ketone or vise versa. Under the consideration that the ring

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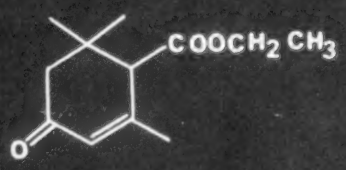
[4] It is highly conceivable that each of these isomers, if so desired, can be specifically prepared by the use of pure cis- or trans-1-bromopropene.



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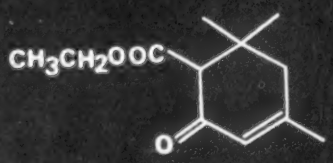

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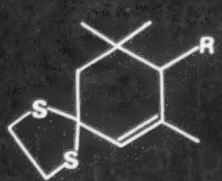
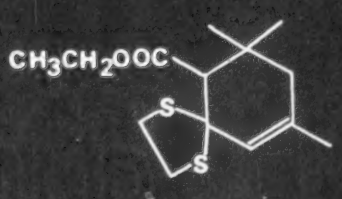


18 R = $COOCH_2CH_3$

20 R = CH_2OH

22 R = CHO



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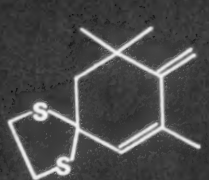

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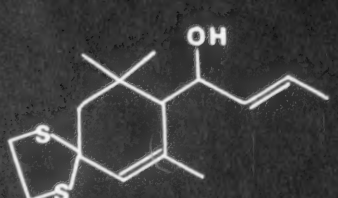

23

double bond might easily move into conjugation with the ketone carbonyl being formed, it was preferable to leave the oxidation to the end of the synthesis. Desulfurization of 24 with Raney nickel was however not promising. Under a variety of conditions, it resulted in a complex mixture of products. Consequently, 23 and 24 were first oxidized to the corresponding ketones 25 and 26. Initial studies using pyridinium chlorochromate according to the procedure of Corey and Suggs (22) gave a multiplex of products. On the other hand, the use of the activated manganese dioxide (23) gave high yields of the desired products. On treatment with a thirty-fold (by weight) excess of manganese dioxide in methylene chloride at room temperature for ten hours, 23 was oxidized smoothly to give a 85% yield of ketone 25 whose ir spectrum showed the α,β-unsaturated ketone absorption band at 1685 cm^{-1}. The trans nature of the double bond[5] was revealed by its nmr spectrum exhibiting a large coupling constant of 15 Hz for the two vicinal vinylic protons at δ 6.80 and 6.21. Under the same reaction conditions, 24 afforded a 45% yield of the expected oxidation product 26 and in addition, 25 in 31% yield. The formation of the latter compound required an isomerization of the side chain double bond. It is worth noting that the isomerization

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[5] The stereochemistry of the oxidation product of 24, as well as those of 23 and 24 follow from this assignment.

process most likely occurred prior to the oxidation since further treatment of 26 with manganese dioxide under the same conditions did not produce any detectable amount of 25. More importantly, when the oxidation of 24 was carried out using a less amount of activated manganese dioxide (twelve-fold excess), it resulted in the exclusive formation of 26 in 91% yield. Thus, under slightly different conditions, cis-alcohol 24 can be used either to provide additional amount of trans-ketone 25 or to form exclusively the corresponding cis-ketone 26.

The thioketal groups of 25 and 26 were finally removed by treatment in 98% ethanol with W-2 Raney nickel (24) which was deactivated in advance in refluxing acetone for eight minutes. Under these conditions, 25 gave exclusively trans-α-damascone (3b) in 56% yield whereas 26 afforded equal amounts of trans- (3b) and cis-α-damascone (3a)[6] in a total yield of 64%. The ir, nmr, and mass spectra of the two α-damascones thus obtained were shown to be identical with those reported in the literature (1).

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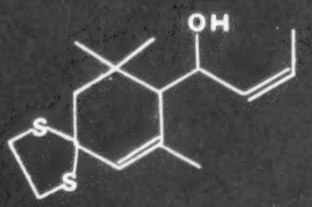
[6] At present, we are unable to effect the desulfurization without partial isomerization of the double bond.



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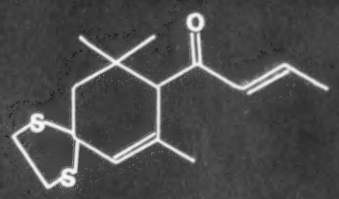

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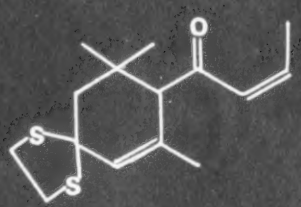

26

EXPERIMENTAL

General

Mass spectra were recorded on A.E.I. MS-50, MS-9 and MS-2 mass spectrometers. Ir spectra were obtained using Perkin-Elmer Models 457 and 337 spectrometers. Nmr spectra were recorded on Varian A-60 and HR-100 spectrometers. Unless otherwise stated, carbon tetrachloride was employed as the solvent and tetramethylsilane as internal standard. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Elemental analyses were performed by the microanalytical laboratory of this department. Melting points were determined on Kofler hot stage apparatus and are uncorrected.

4-Carbethoxy-3,5,5-trimethyl-2-cyclohexen-1-one (16) and 6-Carbethoxy-3,5,5-trimethyl-2-cyclohexen-1-one (17).

The procedure of Rubinstein (15) was used for the boron trifluoride catalysed condensation of ethyl acetoacetate and acetone.

At 0°C, boron trifluoride etherate (290 g, 2 mol) was added dropwise to a well stirred mixture of ethyl acetoacetate (134 g, 1 mol) and acetone (116g, 2 mol). After further stirring at 0°C for 1 h and in a cold room (0-5°C) for 3 days, the resulting solution was poured

onto crushed ice (ca. 500 g) and carefully neutralized with sodium bicarbonate (ca. 200 g). The organic layer was separated and the aqueous solution was extracted twice with ether. The organic solutions were combined and dried first over potassium carbonate and then over magnesium sulfate. Filtration and concentration gave an oil which was distilled. Three fractions (total 55.9 g, 27% yield) collected at 110-115°C/2.5 mm (4.47 g), 116-118°C/2.5 mm (38.11 g), and 119-150°C/2.5 mm (13.32 g) showed practically identical ir and nmr spectra. Their nmr spectra indicated that each fraction consisted of 16 and 17 in a ratio of ca. 2:1. A sample of the mixture (500 mg) was separated by column chromatography on silica gel. Elution with a solution of 10% ether in Skelly B gave 17 (120 mg): ir (film) 1732 (ester), 1675 (ketone) and 1640 cm^{-1} (double bond); nmr (CCl_4) δ 5.81 (m, 1H, =CH-), 4.13 (q, 2H, J = 7 Hz, $-OCH_2-$), 3.00 (s, 1H, $-\underset{|}{\overset{\frown}{C}}HCOO-$), 2.52 (broad d, 1H, J = 18 Hz, $-C\underline{H}(H)\underset{|}{C}=$), 2.03 (broad d, 1H, J = 18 Hz, $-\underset{|}{C}H(H)\underset{|}{C}=$), 1.96 (m, 3H, $=\underset{|}{C}CH_3$), 1.25 (t, 3H, J = 7 Hz, $-CH_2C\underline{H}_3$), 1.10 (s, 3H, CH_3), and 1.05 (s, 3H, CH_3). Further elution with the same solution gave 16 (230 mg): ir (film) 1735 (ester), 1675 (ketone), and 1645 cm^{-1} (double bond); nmr (CCl_4) δ 5.87 (broad s, 1H, =CH-), 4.17 (q, 2H, J = 7 Hz, $-OCH_2-$), 2.92 (broad s, 1H, $-\underset{|}{C}HCOO-$), 2.67 (d, 1H, J = 16 Hz, $-C\underline{H}(H)CO-$), 1.90 (d, 3H, J = 1.5 Hz, $=\underset{|}{C}CH_3$), 1.88 (d, 1H,

J = 16 Hz -C<u>H</u>(H)CO-), 1.27 (t, 3H, J = 7 Hz, -$OCH_2C\underline{H}_3$), and 1.03 (s, 6H, -$\dot{C}(CH_3)_2$).

8-Carbethoxy-7,9,9-trimethyl-1,4-dithiospiro[4.5]dec-6-ene (<u>18</u>).

(A) From Pure <u>16</u>.

At 0°C, to a solution of <u>16</u> (130 mg, 0.62 mmol) in 1,2-ethanedithiol (0.6 ml), was added boron trifluoride etherate (0.1 ml). The resulting solution, after stirring at room temperature for 16 h, was poured into ice-cold 2 N aqueous sodium hydroxide (25 ml) and extracted with chloroform. The chloroform solution was washed with water, dried ($MgSO_4$), filtered and concentrated. Column chromatography of the oil product on silica gel, using benzene as eluent, gave <u>18</u>: ir (film) 1732 (ester) and 1665 cm^{-1} (double bond); nmr (CCl_4) δ 5.63 (broad s, 1H, =CH-), 4.09 (q, 2H, J = 7 Hz, -OCH_2-), 3.28 (s, 4H, -SCH_2CH_2-), 2.63 (d, 1H, J = 14 Hz, -C<u>H</u>(H)-), 2.52 (s, 1H, -$\dot{C}$HCOO-), 1.97 (d, 1H, J = 14 Hz, -C<u>H</u>(H)-), 1.66 (broad s, 3H, =$\dot{C}CH_3$), 1.24 (t, 3H, J = 7 Hz, -$OCH_2C\underline{H}_3$), 1.05 (s, 3H, -CH_3), and 0.95 (s, 3H, -CH_3), mass spectrum M^+ 286.10606 (calcd. for $C_{14}H_{22}O_2S_2^{32}$: 286.10613).

(B) From the Mixture of <u>16</u> and <u>17</u>.

A mixture of <u>16</u> and <u>17</u> (5 g, 23.8 mmole) obtained

from the distillation of the condensation reaction products (vide supra) was dissolved in 1,2-ethanedithiol (20 ml) and at 0°C boron trifluoride etherate (2 ml) was added. After stirring at 0°C for 7 h, the reaction mixture was worked up according to the procedure described above to give an oily product which was purified by column chromatography on silica gel. Elution with benzene gave 18 (4.23 g, ~100% based on 16). Further elution with benzene resulted in the recovery of 17 (1.45 g).

10-Carbethoxy-7,9,9-trimethyl-1,4-dithiospiro[4.5]dec-6-ene (19).

At 0°C, boron trifluoride etherate (0.1 ml) was added to a solution of 17 (120 mg, 0.57 mmole) in 1,2-ethanedithiol (0.5 ml). After stirring at room temperature for 3 h, the resulting solution was worked up in the usual manner. Column chromatography of the crude product on silica gel with benzene elution gave 19: ir (film) 1735 (ester) and 1670 cm^{-1} (double bond); nmr (CCl_4) δ 5.38 (broad s, 1H, =CH-), 4.02 (q, 2H, J = 7 Hz, $-OCH_2-$), 3.20 (s, 4H, $-SCH_2CH_2S-$), 2.92 (s, 1H, $-\overset{|}{C}HCOO-$), 1.65 (broad s, 3H, $=\overset{|}{C}CH_3$), 1.19 (t, 3H, J = 7 Hz, $-OCH_2\underline{C}H_3$), 1.05 (s, 3H, $-CH_3$), and 0.92 (s, 3H, $-CH_3$).

8-Hydroxymethyl-7,9,9-trimethyl-1,4-dithiospiro[4.5]-dec-6-ene (20).

Lithium aluminum hydride (990 mg, 26.05 mmol) was slowly added to a well stirred solution of 18 (5 g, 17.48 mmol) in ether (60 ml) at -78°C. Stirring was continued under an atmosphere of nitrogen at room temperature overnight. After which time, methanol was added dropwise until the evolution of hydrogen gas stopped. Water and saturated aqueous ammonium chloride (30 ml each) were added. The mixture was acidified with 1 N hydrochloric acid to pH 2 and extracted with chloroform. The extracts were washed with water and combined. Drying ($MgSO_4$), filtration, and concentration gave the crude product. Purification of the crude product by silica gel column chromatography using pentane-benzene (1:1) as eluent gave 20 (3.4 g, 82%): m.p. 46-7°C (ether); ir ($CHCl_3$) 3430 (alcohol) and 1650 cm^{-1} (double bond); nmr (CCl_4) δ 5.64 (m, 1H, $=\overset{|}{C}H$), 3.65 (m, 2H, $-OCH_2-$) 3.26 (s, 4H, $-SCH_2CH_2S-$), 1.79 (d, 3H, J = 2 Hz, $=\overset{|}{C}CH_3$), 1.05, and 1.08 (both s, 3H each, $-\overset{|}{C}(CH_3)_2$); mass spectrum M^+ 244.0952 (Calcd. for $C_{12}H_{20}OS_2$: 244.0955).

Anal. Calcd. for $C_{12}H_{20}OS_2$: C, 58.97; H, 8.25; S, 26.24. Found: C, 59.15; H, 8.16; S, 26.07.

8-Formyl-7,9,9-trimethyl-1,4-dithiospiro[4.5]dec-6-ene (22).

To a solution of 20 (153 mg, 0.63 mmol) in dimethyl-

sulfoxide (0.7 ml), were added a solution of dicyclohexylcarbodiimide (400 mg, 1.94 mmol) in benzene (0.35 ml) and a solution of 85% phosphoric acid (4 μℓ) in dimethylsulfoxide (0.4 ml). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 20 h. Ethyl acetate (1.5 ml) and a solution of oxalic acid (153 mg, 1.21 mmol) in methanol (3 ml) were added sequentially and the resulting mixture after stirring at room temperature for 30 min was filtered. The filtrate was added to water and extracted with chloroform. The chloroform solution after washing with saturated aqueous sodium bicarbonate, was dried over magnesium sulfate, filtered and concentrated. The crude product thus obtained was subjected to preparative thin-layer chromatography using silica gel as adsorbant and a solution of 20% ether in petroleum ether as eluent to give 22 (122 mg, 80%): m.p. 62-3°C (ether); ir (film) 2730, 1715 (aldehyde), and 1648 cm^{-1} (double bond); nmr (CCl_4) δ 9.39 (d, 1H, J = 5 Hz, -CHO), 5.79 (m, 1H, =CH), 2.39 (s, 4H, $-SCH_2CH_2S-$), 2.46, 2.19 (both d, 1H each, J = 15 Hz, $-CH_2-$), 2.28 (d, 1H, J = 5 Hz, $-\underset{|}{C}H\underline{C}HO$), 1.67 (d, 3H, J = 1.5 Hz, $=\underset{|}{C}CH_3$), 1.07 and 1.04 (both s, 3H each, $-\underset{|}{C}(CH_3)_2$); mass spectrum M^+ 242.0799 (Calcd. for $C_{12}H_{18}OS_2$: 242.0799).

Anal. Calcd. for $C_{12}H_{18}OS_2$: C, 59.46; H, 7.48. Found: C, 59.37; H, 7.39.

Trans- (23) and Cis-1-(2,6,6-trimethyl-4,4-ethylenedithio-2-cyclohexenyl)-2-buten-1-ol (24).

To a suspension of magnesium turnings (60 mg, 2.96 g-atom) in tetrahydrofuran (6 ml), was added a solution of cis- and trans-1-bromo-1-propene (obtained from Aldrich; 0.25 ml) in tetrahydrofuran (1 ml). The mixture was refluxed under a nitrogen atmosphere for 45 min and cooled to -10°C. A solution of 22 (418 mg, 1.73 mmol) in tetrahydrofuran (5 ml) was introduced. After stirring at -5°C for 2 h and at room temperature for an additional 2 h, the reaction mixture was filtered. The filtration was poured into saturated aqueous ammonium chloride and extracted with chloroform. Work-up of the extracts in the usual manner gave an oil which was purified by silica gel preparative thin-layer chromatography. Elution with ethyl-petroleum ether (1:1) gave 24 (234 mg, 48%; slower moving) and 23 (220 mg, 45%). 24, m.p. 93-4°C (ether), showed the following spectral data: ir (CCl_4) 3540 (alcohol) and 1650 cm^{-1} (double bond); nmr (CCl_4) δ 5.79 (d, 1H, J = 1.5 Hz, $-\underset{|}{C}=CH$), 5.38 (m, 2H, -CH=CH-), 4.68 (m, 1H, $-\underset{|}{C}\underline{H}OH$), 3.24 (s, 4H, $-SCH_2CH_2S-$), 1.79 (d, 3H, J = 1.5 Hz, $=\underset{|}{C}CH_3$), 1.67 (d, 3H, J = 5 Hz, $=CH\underline{C}H_3$), 1.11 and 1.01 (both s, 3H each, $-\underset{|}{C}(CH_3)_2$); mass spectrum M^+ 284.1251 (Calcd. for $C_{15}H_{24}OS_2$: 284.1269).

Anal. Calcd. for $C_{15}H_{24}OS_2$: C, 63.33; H, 8.50; S, 22.54. Found: C, 63.25; H, 8.38; S, 22.39.

The following spectral data were obtained for 23: ir (film) 3470 (alcohol) and 1645 cm^{-1} (double bonds); nmr (CCl_4) δ 5.52 (m, 2H, -CH=CH-), 5.21 (broad s, 1H, $-\underset{|}{C}=CH-$), 4.36 (m, 1H, $-\underset{|}{C}\underline{H}OH$), 3.27 (s, 4H, $-SCH_2CH_2S-$), 1.75 (d, 3H, J = 2 Hz, $=\underset{|}{C}CH_3$), 1.67 (m, 3H, $=CHC\underline{H}_3$), 1.05 and 0.99 (both s, 3H each, $-\underset{|}{C}(CH_3)_2$); mass spectrum M^+ 284.1255 (Calcd. for $C_{15}H_{24}OS_2$: 284.1269).

7,9,9-trimethyl-8-(trans-1-oxo-2-butenyl)-1,4-dithiospiro-[4.5]dec-6-ene (25).

Alcohol 23 (600 mg, 2.11 mmol) was dissolved in methylene chloride (120 ml) and activated manganese dioxide (18 g) was added. The mixture was stirred at room temperature for 10 h and filtered. Concentration of the filtrate gave an oil. Preparative thin layer chromatography (silica gel) of the oil eluting with a solution of 20% ether in n-pentane afforded 25 (501 mg, 85%): ir (film) 1685 (ketone), 1665 (double dond), and 1625 cm^{-1} (double bond); nmr (CCl_4) 6.80 (qd, 1H, J = 15, J' = 6.5 Hz, $=C\underline{H}CH_3$); 6.21 (qd, 1H, J = 15, J' = 1.5 Hz, -COCH=), 5.69 (broad s, 1H, $-\underset{|}{C}=CH-$), 3.29 (s, 4H, $-SCH_2CH_2S-$), 1.90 (dd, 3H, J = 6.5, J' = 1.5 Hz, $=CHCH_3$), 1.62 (d, 3H, J = 2Hz, $=\underset{|}{C}CH_3$), 0.86 and 1.07 (both s, 3H each $-C(\underset{|}{C}H_3)_2$); mass spectrum M^+ 282.1113 (Calcd. for $C_{15}H_{22}OS_2$: 282.1113).

Anal. Calcd. for $C_{15}H_{22}OS_2$: C, 63.78; H, 7.85; S, 22.70. Found: C, 63.83; H, 7.72; S, 22.51.

7,9,9-trimethyl-8-(cis-1-oxo-2-butenyl)-1,4-dithiospiro-[4.5]dec-6-ene (26).

Activated manganese dioxide (3.7 g) was added to a solution of 24 (300 mg, 1.06 mmol) in methylene chloride (80 ml). The reaction mixture was stirred at room temperature for 6 h. Filtration and concentration gave an oil which was purified by preparative thin-layer chromatography on silica gel. Elution with a solution of 20% ether in n-pentane afforded 26 (273 mg, 91%); ir (film) 1680 cm^{-1} (ketone), 1655 (double bond), and 1610 cm^{-1} (double bond); nmr (CCl_4) δ 6.16 (m, 2H, -CH=CH-), 5.67 (broad s, 1H, =CH-), 3.26 (s, 4H, $-SCH_2CH_2S-$), 2.07 (m, 3H, $=CHCH_3$), 1.63 (d, 3H, J = 2 Hz, $=\overset{|}{C}CH_3$), 1.07 and 0.99 (both s, 3H each, $-\overset{|}{C}(CH_3)_2$); mass spectrum M^+ 282.1112 (Calcd. for $C_{15}H_{22}OS_2$: 282.1112).

trans-α-Damascone (3b).

A suspension of W-2 Raney Nickel (2 ml) in acetone (5 ml) was refluxed for 8 min. After acetone was removed by a pipet, a solution of 25 (52 mg, 0.18 mmol) in 98% ethanol (10 ml) was added and the resulting mixture was stirred at room temperature for 10 min. Filtration,

and concentration followed by preparative thin-layer chromatography of the crude product on silica gel with ether-petroleum ether (1:9) elution gave 3b (20 mg, 56%): ir (film) 1690 (ketone), 1662 (double bond), and 1628 cm^{-1} (double bond); nmr (CCl_4) δ 6.77 (qd, 1H, J = 15.5, J' = 6.5 Hz, $=C\underline{H}CH_3$), 6.18 (qd, 1H, J = 15.5, J' = 1.5 Hz, -COCH=), 5.52 (m, 1H, =CH-), 2.75 (broad s, 1H, $-\overset{|}{C}HCO-$), 1.88 (dd, 3H, J = 6.5, J' = 1.5 Hz, $=CHC\underline{H}_3$), 1.55 (t, 3H, J = 1.5 Hz, $=\overset{|}{C}CH_3$), 0.92, and 0.83 (both s, 3H each, $-\overset{|}{C}(CH_3)_2$).

cis-α-Damascone (3a).

A solution of 26 (60 mg, 0.21 mmol) in 98% ethanol (10 ml) was added to the deactivated (by the same procedure described in the previous experiment) W-2 Raney nickel (2 ml) and the resulting mixture was stirred at room temperature for 1.5 h. The mixture was filtered and the filtrate concentrated. Preparative thin-layer chromatography of the oily product on silica gel using a solution of 10% ether in n-pentane as eluent gave 3a (faster-moving; 13 mg, 32%) and 3b (13 mg, 32%). cis-α-Damascone (3a) thus obtained showed the following spectral data: ir (film) 1685 (ketone), 1673 (double bond) and 1615 cm^{-1} (double bond); nmr 6.14 (m, 2H, -CH=CH-), 5.50 (m, 1H, =CH-), 2.67 (broad s, 1H, $-\overset{|}{C}HCO-$), 2.05 (d, 3H, J = 6 Hz, $=CHC\underline{H}_3$), 1.55 (t, 3H, J = 1.5 Hz, $=\overset{|}{C}CH_3$), 0.91 and 0.85 (both s, 3H each $-\overset{|}{C}(CH_3)_2$).

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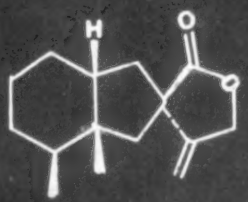
INTRODUCTION

In 1968, Naya and his co-workers reported the isolation, from the flower stalks of the Japanese wild butterburs, Petasites japonicus Maxim. (Japanese name "Fuki"), of several novel sesquiterpenoids, fukinanolide (1), fukinolide (2) and S-fukinolide (3), homofukinolide (4) and dihydrofukinolide (5), based on a modified eremophilane skeleton of fukinane (6) (1-3). At about the same time compounds 1, 2, and 3 were also obtained along with bakkenolide-D (7) and -E (structure yet to be reported) from the bud of Petasites japonicus subsp. giganteus Kitam by Kitahara, et al. who named them respectively bakkenolide-A, -B, and -D based on the local name "Bakke" for the bud of that plant (4-7).

The structure of fukinanolide (bakkenolide-A) (1), the simplest member of the fukinane family, was deduced by its chemical degradation and by extensive spectroscopic studies independently by the aforementioned two Japanese groups (1, 4, 7). The correlation of 1 and fukinone (8), whose absolute configuration had previously been determined (8), via fukinan-8-ol (9) (1) and ketone 10 (4, 7) further allowed these workers to assign its absolute stereochemistry as shown.

Shortly after the identification of 1 and the related natural products, the parent hydrocarbon 6 in optically active form was synthesized from fukinone 8



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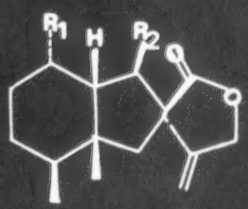
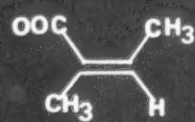
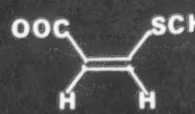
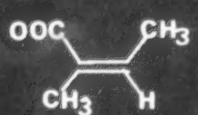


2 R_1 =  ; R_2 = OAc

3 R_1 =  ; R_2 = OAc

4 $R_1 = R_2$ = 

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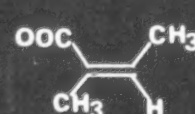
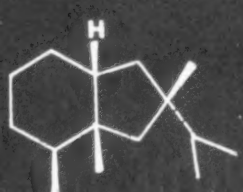
7 R_1 =  ; R_2 = OH



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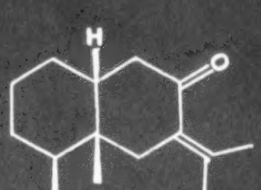

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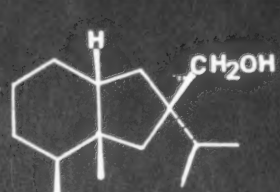
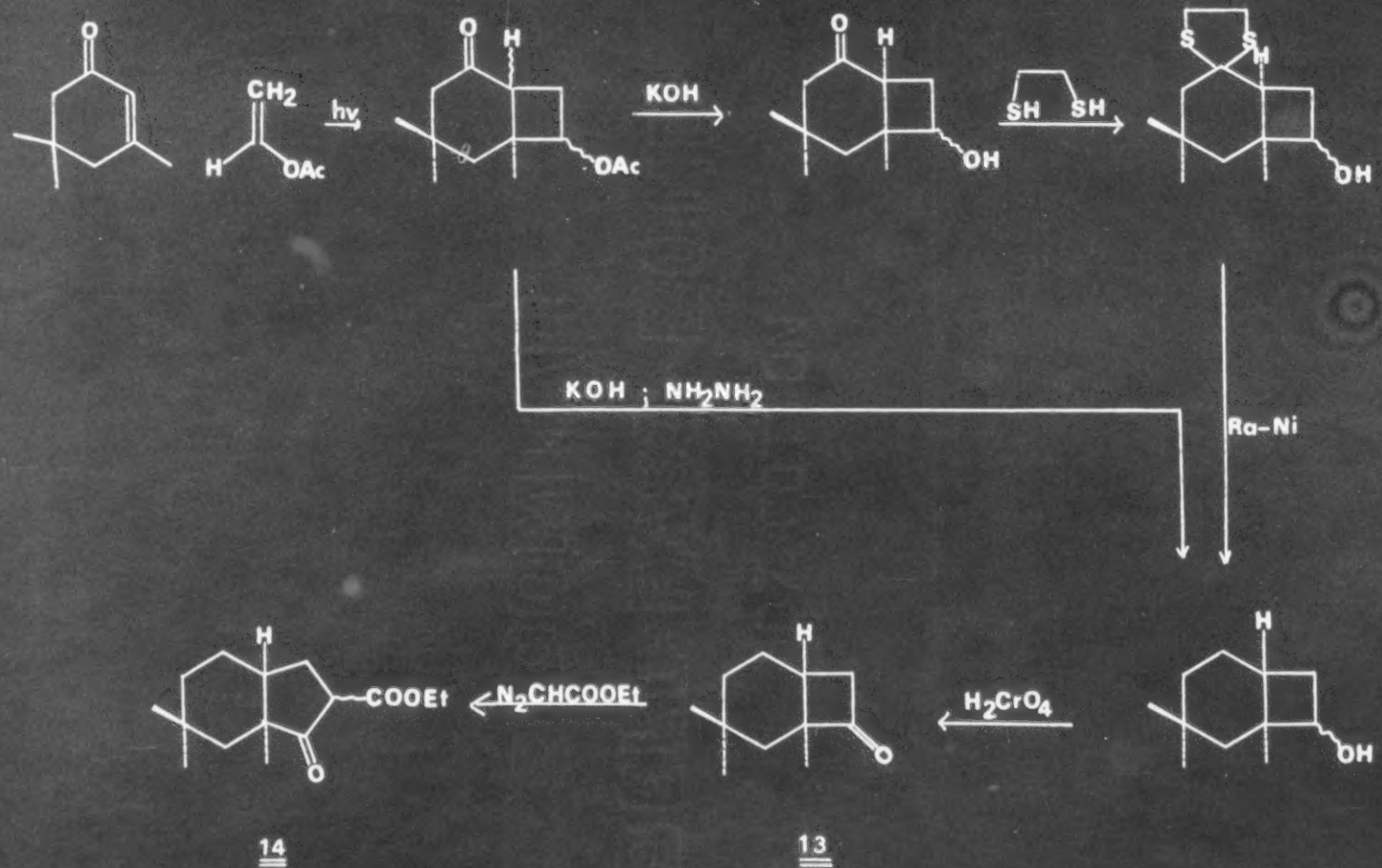


9

via intermediate 9 (9). Recently a total synthesis of racemic fukinanolide (1) has been achieved from 2,3-dimethylcyclohexanone involving the transformation of 11→12 as a key step (10).

Our approach to 1 is based on the new method developed in this laboratory for the synthesis of hydrindanonecarboxylate system (11). The method involves, as illustrated with isophorone in Scheme I, two important stages - the construction of a bicyclo[4.2.0]-octanone system from a cyclohexenone and the expansion of the derived cyclobutanone ring. The usefulness of this method in the synthesis of 1 is quite obvious. By a suitable choice of starting material, i.e., 3,4-dimethyl-2-cyclohexen-1-one, it should effect the construction of the parent hydroindane ring system of 1 in a simple manner with concomitant incorporation of the required methyl groups and the resulting β-keto ester moiety is highly suitable for subsequent manipulation. Furthermore, by vitue of the mode of the transformations, the method allows the exclusive formation of a cis ring juncture which is required for 1. It was also noted during the development of the method that the boron trifluoride catalysed ring expansion of biclo[4.2.0]-octan-7-ones with diazoacetic ester to the corresponding hydrindanonecarboxylates, e.g. 13→14, proceeded in a highly regioselective manner and the general migratory

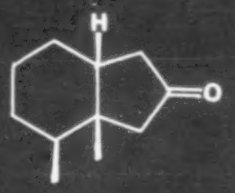


14 13

SCHEME 1

aptitude was shown to be such that wherever applicable the less substituted α-carbon migrates predominantly or exclusively. This salient feature further facilitates the synthetic planning.

The second part of this thesis describes the preparation, from 3,4-dimethyl-2-cyclohexen-1-one, of keto ester 15 which should prove to be a useful intermediate for a total synthesis of (±)-fukinanolide (1).



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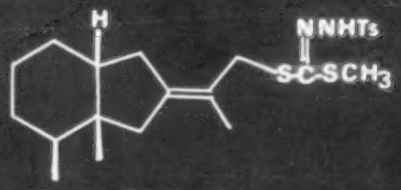

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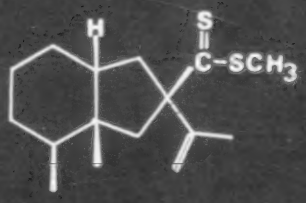

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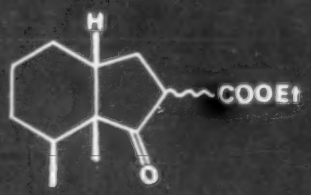

15

RESULTS AND DISCUSSION

The synthesis of keto ester 15, a potential precursor of fukinanolide (1), resembles that of 14 shown in Scheme I. In order to introduce the required methyl substituents, 3,4-dimethyl-2-cyclohexen-1-one was chosen as the starting material. The enone was readily prepared by Birch reduction (12) of 3,4-dimethylanisole followed by the acid treatment of the resulting enol ester 16. The anisole in turn was obtained by methylation of the corresponding phenol using methyl iodide and potassium carbonate.

Photocycloaddition of 3,4-dimethyl-2-cyclohexen-1-one to vinyl acetate in benzene gave an 82% yield of the adduct 17 consisting of at least four diastereomers as indicated by its nmr spectrum displaying four singlets at δ 2 region for a total of three acetoxy protons. The relative orientation of its functionalities follows unambiguously from further transformations. Since two (marked with *) of the four chiral centers present in the molecule will be either possibly epimerized or destroyed in the later stage, no attempt was made to separate the isomeric compounds.

Subsequent hydrolysis of 17 with aqueous sodium hydroxide in methanol at reflux afforded a diastereomeric mixture of keto alcohol 18 in 87% yield. The ir spectrum showed strong hydroxyl and ketone absorption bands at

3400 and 1705 cm^{-1} respectively. The nmr spectrum was rather complex due to the isomeric nature of the material but clearly indicated the presence of a total of one methine proton adjacent to the hydroxyl group and a total of six methyl protons. A molecular ion peak at 168.1152 in the mass spectrum was in agreement with the structural assignment. The ring juncture of 18 could be readily assigned as cis, since it has been well established that in the bicyclo[4.2.0]octan-2-one systems, the trans ring juncture (if present in the precursor) is readily epimerized upon treatment with base to give the thermodynamically more stable cis form (13).

Thioketalization of 18 using 1,2-ethanedithiol and boron trifluoride etherate resulted in the formation of thioketal alcohol 19 in 82% yield. One of the diastereomers of 19 was isolated in pure form and the others as a mixture. The single isomer showed, in the ir spectrum, absorption bands at 3584 and 3440 cm^{-1} for the hydroxyl group and, in the nmr spectrums, a triplet at δ 3.93 for the proton adjacent to the hydroxyl group, and a multiplet at δ 3.20 for the four thioketal methylene hydrogens. A singlet at δ 1.18 and a doublet at 1.07 were also observed for the two methyls. The ir spectrum of the isomeric mixture displayed the hydroxyl absorption at 3600 cm^{-1}. Its nmr spectrum was rather complex and could not be diagnosed in details because

of the presence of likely all three other possible isomers of 19 but showed the general features in accord with the assigned structure.

For the subsequent removal of the thioketal group, all the isomers of 19 were used. The desulfurization reaction was effected by W-4 Raney nickel (14) in ethanol at room temperature and the diastereomeric mixture of alcohol 20 thus obtained in 86% yield showed the complete absence of the thioketal signals in the nmr spectrum.

Moffatt oxidation (15) of 20 with dicyclohexylcarbodiimide, dimethylsulfoxide, phosphoric acid in benzene gave rise to, in a total yield of 67% and in ca. 1:1 ratio, two isomeric ketones 21 and 22[1] which were readily separable by column chromatography. The isomeric relationship of these two compounds was clearly indicated by their mass spectra. In each case, a molecular ion peak consistent with $C_{10}H_{16}O$ was observed. The ir spectra showed, in both cases, an absorption band at 1765 cm^{-1} for the four-membered ketone. In the nmr spectrum of 21, the angular methyl appeared as a singlet at δ 1.26 and the other methyl group resonated at 1.03 as a doublet. Whereas in that of 22, the corresponding methyls were displayed respectively at δ 1.01, a singlet,

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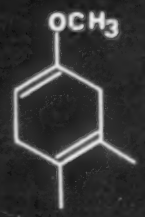
[1] Jones oxidation of 20 gave, in addition to 21 and 22, a substantial amount of lactone 23.



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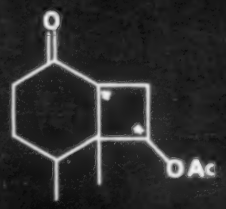

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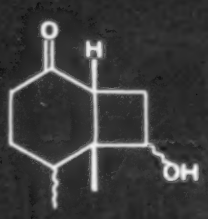

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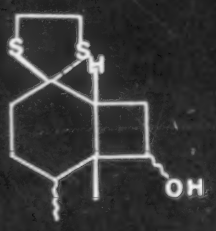

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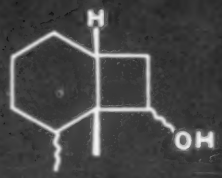

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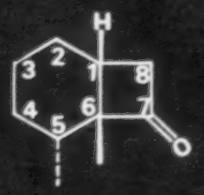

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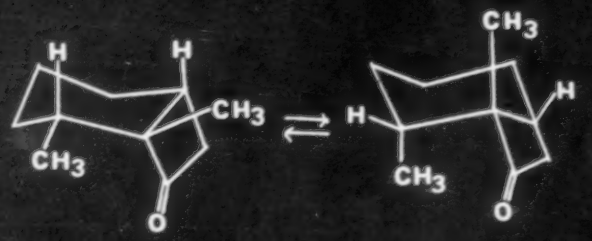
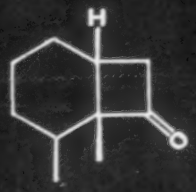


21a 21b



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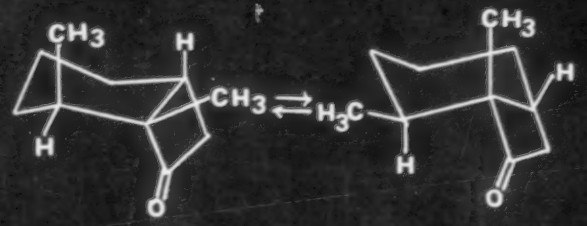
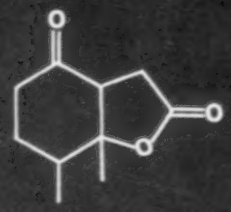


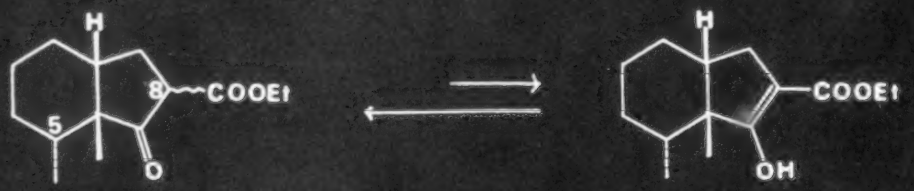
22a 22b



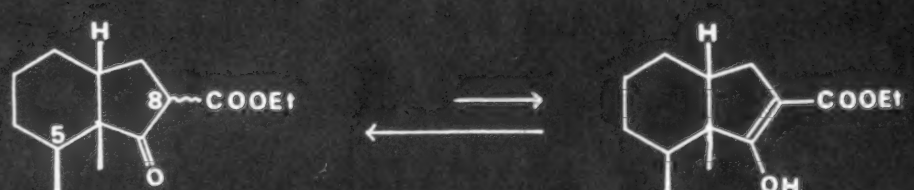
23

and δ 0.89, a doublet. In addition to supporting the assigned structures, these nmr features further provided valuable information for the deduction of the stereochemistry of these two compounds. Of the two possible conformations, 21a and 21b, of 21 with the six-membered ring existing in the chair form, 21a is considerably more stable in light of the total number of equatorial substituents with respect to the cyclohexane ring. Furthermore, an examination of dreiding models reveals that the methyl on C-5 lies close to and within the deshielding zone of the ketone carbonyl. A down-field shift of the C-5 methyl is thus expected. On the other hand, the C-5 methyl of 22 is projected away from the deshielding-plane of the carbonyl in both of the two corresponding conformations which are probably of similar stability and is expected to appear in the nmr spectrum at a normal position. As a consequence of these considerations, the compound with the methyl doublet at δ 1.03 could be tentatively assigned as trans and the other with that at δ 0.89 as cis. These assignments were found to be consistent with those of the following ring expansion products.

On treatment with boron trifluoride etherate and ethyl diazoacetate (11), 21 underwent ring expansion smoothly and in a highly regioselective manner to give, in 83% yield, keto ester 24 existing partially in its



24 24a



15 15a

enol form 24a (~30%). Similarly, the boron trifluoride catalysed homologation of 22 with ethyl diazoacetate resulted in the formation of 15 (92% yield) containing both epimers and existing partially in the enol form 15a. The structures of 24 and 15 were evident from their spectral data. In the mass spectra, both displayed the expected molecular ion peaks at 238. In the ir spectrum, 24 showed, in addition to those for the ester and the ketone carbonyls at 1745 and 1720 cm^{-1} respectively, absorption bands at 3420 (enol), 1650 (ester), and 1620 (double bond) for the corresponding enol form 24a. Similarly, two sets of absorption bands were observed at 1745 and 1725 cm^{-1} and at 3450, 1645 and 1605 cm^{-1} for 15 in its ir spectrum. Of special significance were the nmr spectra of these two isomers. The triplet at δ 3.16 for the C-8 proton of 24 and the two doublets of doublets at δ 3.31 and 3.06 for that of 15 clearly defined the locations of their ester groups. The appearance of two doublets of doublets for a C-8 proton coupled with the fact that three singlets were observed at δ 0.99, 0.97 and 0.95 for the methyl on C-6 in the nmr spectrum of 15 further indicated that both the C-8 epimers of 15 were present. Moreover, an examination of the dreiding models indicated that the same stereochemical considerations applied to ketones 21 and 22 (vide supra) could be extended to the corresponding ring expansion

products. As a consequence, it was anticipated that, in the nmr spectra, the C-5 methyl substituent in the product derived from trans-ketone 21 should exert a noticeable down-field shift with respect to that in the product derived from the corresponding cis compound 22. Indeed, the C-5 methyl of 24 appeared in the nmr spectrum at δ 1.23 as a doublet whereas 15 showed two doublets (due to either the epimeric pair or the enol form) at δ 0.79 and 0.73 for the corresponding substituent.

The acquisition of keto ester 15 represents our current advance towards the total synthesis of fukinanolide (1). To complete the synthesis, it remains to install the interesting β-methylene-γ-lactone system present in 1 by modifying the versatile β-keto ester group of 15.

EXPERIMENTAL

General

Spectra and elemental analyses were obtained and reported as indicated in the Experimental section of Part I. Ir samples if not specified were run as thin films. Silica gel was used as an adsorbant in all cases where column chromatography was used for purification.

3,4-Dimethylanisole

A mixture of 3,4-dimethylphenol (156.95 g, 1.28 mol) and potassium carbonate (314 g, 2.27 mol) in acetone (974 ml) was stirred at room temperature for 3 h. Methyl iodide (314 g, 2.21 mole) was added. Stirring was continued for 16 h and the reaction mixture was filtered. The filtrate was concentrated to ca. 250 ml. Water (80 ml) was added and the resulting mixture extracted with ether (3 x 300 ml). The organic solution was washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and filtered. Evaporation of the solvent followed by the distillation of the crude oily product under reduced pressure using a 25 cm Vigreux column gave 49.18 g of the starting material and 109.79 g (91% based on the consumed starting material) of 3,4-dimethylanisole: b.p. 45-7°C/1 mm; ir, 1605 and 1580 cm^{-1} (aromatic); nmr (CCl_4) δ 6.96-6.43 (m, 3H, aromatic), 3.52 (s, 3H, $-OCH_3$), and

2.05 (s, 6H, methyls).

3,4-Dimethyl-2-cyclohexen-1-one

At -78°C and under a nitrogen atmosphere, a solution of 3,4-dimethylanisole (50 g, 0.37 mol) in ether (870 ml) and tert-butyl alcohol (870 ml) was added to freshly distilled ammonia (1.785 ℓ) over a period of 50 min. Lithium (42 g, 6 g-atom) was added in small portions (ca. 2 g each) over a 40 min period. After further stirring for 5 h, methanol (350 ml) was added dropwise to the reaction mixture and ammonia was allowed to evaporate at room temperature. Water (2 ℓ) was added and the organic layer separated. The aqueous solution was extracted with ether (3 x 500 ml). The organic solution was washed with saturated aqueous sodium chloride, and concentrated to a volume of ca. 100 ml. A small sample was further concentrated to give 16 which showed the following nmr spectrum (CCl_4): δ 4.44 (m, 1H, =CH-), 7.43 (s, 3H, OCH_3), 2.57 (m, 4H, $-CH_2\overset{|}{C}=CHCH_2-$), and 1.59 (s, 6H, methyls). The reaction was repeated using 59.79 g (0.415 mol) of the starting material.

The crude reaction products from the two runs were combined and dissolved in methanol (750 ml) and water (80 ml). Concentrated hydrochloric acid (15 ml) was added and the reaction mixture refluxed under a nitrogen

atmosphere for 1 h. The volume of the resulting solution was reduced to ca. 200 ml under aspirator pressure. The residue was diluted with water (300 ml), carefully neutralized with sodium carbonate and extracted with methylene chloride (3 x 300 ml). Work-up of the organic solution in the usual manner followed by distillation of the crude product using a 25 cm column packed with helices gave 3,4-dimethyl-2-cyclohexen-1-one (50.18 g, 50%): b.p. 44-6°C/1 mm; ir 1670 (ketone) and 1620 cm^{-1} (double bond); nmr (CCl_4) δ 5.66 (m, 1H, olefinic), 1.95 (dd, J < 1, J' < 1 Hz, $=CCH_3$), and 1.18 (d, 3H, J = 7 Hz, $-CH_3$).

7-Acetoxy-5,6-dimethylbicyclo[4.2.0]octan-2-one (17)

A solution of 3,4-dimethyl-2-cyclohexen-1-one (30 g, 0.242 mol) and vinyl acetate (550 ml) in benzene (850 ml) was irradiated at room temperature using a 450 W Hanovia high-pressure quartz mercury-vapor lamp and a Pyrex filter for 20 h during which time a stream of nitrogen gas was maintained to agitate the solution. Concentration of the resulting solution gave a viscous oil which was distilled to give a diastereomeric mixture of 17 (41.59 g; 82%): b.p. 117-9°C/1.5 mm; ir 1735 (ester) and 1710 cm^{-1} (ketone); nmr (CCl_4) 5.50-4.50 (complex, 1H, $-CHOAc$), 1.99, 1.97, 1.96, 1.93 (all s, total 3H, $-OCH_3$), and 1.31-0.8 (complex, 6H, methyls);

mass spectrum M^+ 210.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.25; H, 8.67.

7-Hydroxy-5,6-dimethylbicyclo[4.2.0]octan-2-one (18).

To a solution of 17 (10 g, 47.62 mmol) in methanol (100 ml) and water (20 ml), sodium hydroxide (5 g) was added. The reaction mixture was refluxed for 1 h and most of methanol was removed under reduced pressure. The residue was diluted with water (180 ml) and extracted with ether (150 ml and 2 x 100 ml). The ether solution was washed twice with saturated aqueous sodium chloride, dried ($MgSO_4$), filtered and concentrated. The residue was distilled to give 18 (6.97 g, 87%): b.p. 120-30°C/ 1.5 mm; ir 3400 (alcohol) and 1705 cm^{-1} (ketone); nmr (CCl_4) δ 4.28-3.67 (complex, 1H, -CHOH), 4.17 (s, 1H, -OH), and 1.25-0.87 (complex, 6H, methyls); mass spectrum M^+ 168.1152 (Calcd. for $C_{10}H_{16}O_2$: 168.1150).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52. Found: C, 71.16; H, 9.47.

2,2-Ethylenedithio-5,6-dimethyl-bicyclo[4.2.0]octan-7-ol (19).

At 0°C keto alcohol 18 (3 g, 17.86 mmol) was dissolved in 1,2-ethanedithiol (12 ml) and boron trifluoride etherate (0.5 ml) was added. The reaction mixture after

stirring under a nitrogen atmosphere for 16 h was poured into ice-cold 2N aqueous sodium hydroxide (120 ml) and extracted with ether (3 x 120 ml). The ether solution was washed with 2 N NaOH and water (120 ml each) and worked up in the usual manner. The crude product was purified by column chromatography. Elution with petroleum ether-benzene (1:1) gave one of the isomers of 19 (390 mg): ir ($CHCl_3$) 3584 and 3440 cm^{-1} (alcohol); nmr (CCl_4) δ 3.93 (t, 1H, J = 7 Hz, -CHOH), 3.20 (m, 4H, $-SCH_2CH_2S-$), 1.18 (s, 3H, $-CH_3$) and 1.07 (d, 3H, J = 6 Hz, $-CH_3$); mass spectrum M^+ 244.0952 (Calcd. for $C_{12}H_{20}OS_2^{32}$ = 244.0956).

Further elution with the same solvent system gave a mixture of 19 (3.20 g): ir 3600 cm^{-1} (alcohol); nmr 4.17 (broad s, total ~1½H, -CHOH), 3.65 (broad d, ~½H, J = 5 Hz, -CHOH), 3.20 (broad s, 4H, $-SCH_2CH_2S-$), and 1.12-0.73 (complex, 6H, methyls); mass spectrum 244.0948.

The total yield of 19 was 82%.

5,6-Dimethylbicyclo[4.2.0]octan-7-ol (20).

A mixture of 19 (3.84 g, 15.7 mmol) and freshly prepared W-4 Raney nickel (38.4 ml) (14) in 98% ethanol (100 ml) was stirred at room temperature under a nitrogen atmosphere overnight. The resulting mixture was carefully filtered and the residue washed several times with

ethanol. The filtrate was passed through a silica gel column and the column washed several times with ether. The organic solution after concentration gave an oil which was purified by column chromatography. Elution with a solution of 15% benzene in Skelly B gave a diastereomeric mixture of 20 (2.08 g, 86%): ir 3390 cm^{-1} (alcohol); nmr (CCl_4) δ 4.33-3.62 (complex, 1H, -CHOH), 3.55 (broad s, 1H, -OH), and 1.07-0.68 (complex, 6H, methyls); mass spectrum M^+ 154.1362 (Calcd. for $C_{10}H_{18}O$: 154.1357).

trans- (21) and cis-5,6-Dimethylbicyclo[4.2.0]octan-7-one (22).

To a solution of 20 (730 mg, 4.74 mmol) in dimethyl sulfoxide (5.5 ml), were added a solution of dicyclohexylcarbodiimide (3 g, 14.5 mmol) in benzene (2.8 ml) and phosphoric acid (0.03 ml). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 22 h. Ethyl acetate (7.8 ml) and a solution of oxalic acid (0.78 g) in methanol (1 ml) were carefully added. After stirring for 30 min, the mixture was filtered and the filtrate was extracted with chloroform and washed with saturated sodium bicarbonate. Drying ($MgSO_4$), filtration, and concentration gave the crude product which was subjected to column chromatography. Elution with benzene-petroleum

ether (1:8) afforded 21 (220 mg, 31%): ir 1765 cm^{-1} (ketone); nmr 3.15 (dd, 1H, J = 17, J' = 8 Hz, $-COC\underline{H}(H)-$), 2.43 (dd, 1H, J = 17, J' = 4 Hz, $-COC\underline{H}(H)-$), 1.26 (s, 3H, $-\overset{|}{\underset{|}{C}}\underline{C}H_3$), and 1.03 (d, 3H, J = 6 Hz, $-\overset{|}{C}H\underline{C}H_3$); mass spectrum M^+ 1.52.1199 (calcd. for $C_{10}H_{16}O$: 152.1201).

Further elution with the same solvent system gave a mixture of 21 and 22 (ca. 1:1, 70 mg, 10%) and pure 22 (190 mg, 26%): ir 1765 cm^{-1} (ketone); nmr (CCl_4) δ 3.08 (dd, 1H, J = 16, J' = 8 Hz, $-COC\underline{H}(H)-$), 2.79 (dd, J = 16, J' = 8 Hz, $-COC\underline{H}(H)-$), 1.01 (s, 3H, $-\overset{|}{\underset{|}{C}}\underline{C}H_3$), and 0.89 (dd, 3H, J = 7, J' = 1 Hz, $-\overset{|}{C}H\underline{C}H_3$); mass spectrum M^+ 152.1205 (Calcd. for $C_{10}H_{16}O$: 152.1201).

trans-8-Carbethoxy-5,6-dimethylbicyclo[4.3.0]nonan-7-one (24).

At 0°C, to a solution of 21 (420 mg, 2.76 mmol) in ether (5 ml) were added a solution of borontrifluoride etherate (784 mg, 5.52 mmol) in ether (2 ml) and a solution of ethyl diazoacetate (630 mg, 5.52 mmol) in ether (2 ml). After stirring at room temperature under an atmosphere of nitrogen for 1.5 h, the resulting solution was cooled to 0°C, carefully made basic with aqueous sodium bicarbonate, and extracted with chloroform. The chloroform solution was washed twice with ice cold 2 N HCl and water, dried ($MgSO_4$), filtered, and concentrated. Column chromatography of the residue

using a solution of 5% ether in benzene gave 24 (547 mg, 83%): ir 3420 (enol), 1745 (ketone), 1720 (saturated ester), 1650 (unsaturated ester) and 1620 cm^{-1} (enol double bond); nmr (CCl_4) δ 10.65 (s, ~1/3H, =COH), 4.16, 4.12 (both q, total 2H, J = 7.5 Hz each, $-OCH_2-$), 3.16 (t, ~2/3H, J = 9 Hz, -COCH-), 1.30, 1.28 (both t, total 3H, J = 7.5 Hz each, $-CH_2CH_3$), 1.23 (d, 3H, J = 6 Hz, $-CHCH_3$) and 1.20 (s, 3H, CH_3); mass spectrum M^+ 238.

cis-8-Carbethoxy-5,6-dimethylbicyclo[4.3.0]nonan-7-one (15).

The ring expansion of 22 and the purification of the product were carried out in the same manner as described in the above experiment. From 22 (338 mg, 2.22 mmol), boron trifluoride etherate (640 mg, 4.44 mmol) and ethyl diazoacetate (507 mg; 4.44 mmol), 487 mg (92%) of 15 was obtained. It showed the following spectral data: ir 3450 (enol), 1745 (ketone), 1725 (ester), 1645 (unsaturated ester) and 1605 (enol double bond); nmr (CCl_4) δ 4.15, 4.11 (both q, total 2H, J = 7 Hz each, $-OCH_2-$), 3.31 (dd, ~0.2H, J = 6, J' = 5 Hz, -COCH-), 3.06 (dd, ~0.8H, J = 10, J' = 8 Hz, -COCH-), 1.29, 1.28 (both t, total 3H, J = 7 Hz each, $-CH_2CH_3$), 0.99, 0.97, 0.96 (all s, total 3H, $-CCH_3$), 0.79 and 0.73 (both d, total 3H, J = 6 Hz each, $-CHCH_3$); mass spectrum M^+ 238.1587 (calcd. for $C_{14}H_{22}O_3$: 238.1569).

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